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Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

DRAFT GUIDANCE FOR INDUSTRY ON
CONTENT AND FORMAT FOR GERIATRIC LABELING

DOCKET No. 98D-1169

Dear Sir or Madam:

Wyeth-Ayerst Laboratories, a Division of American Home Products Corporation, respectfully submits the enclosed comments on the Food and Drug Administration's draft guidance for industry, "Content and Format for Geriatric Labeling."

Wyeth-Ayerst Laboratories is a major research-oriented pharmaceutical company, with leading products in the areas of women's health care, cardiovascular disease therapies, central nervous system drugs, anti-inflammatory agents, vaccines, and generic pharmaceuticals. American Home Products Corporation is one of the world's largest researched-based pharmaceutical and health care products companies. It is a leader in the discovery, development, manufacturing and marketing of prescription drugs and over-the-counter medications.

Comment One

Section II., Background, of the geriatric labeling guidance discusses the types of labeling supplements which require prior approval by the FDA (Attachment 1). Exceptions to this requirement include the incorporation into the package insert of language to add or strengthen instructions for the safe use of a medicinal product [drug - § 314.70(c) (2) or a biological agent - § 610.12(f) (2)]. Revised labeling to advise that there is insufficient data to determine whether responses to drugs and biological products differ between geriatric patients and younger patients is also categorized as a labeling change that may be initiated without prior approval by the FDA [21 CFR 201.57(f) (10) (ii) (A)].

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We respectfully submit that there are two other categories of "Geriatric use" labeling changes which should be permitted without the need for prior approval by representatives of the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research.

21 CFR 201.57 (f) (10) (ii) (B) indicates that product labeling should note when clinical studies with sufficient numbers of geriatric patients did not demonstrate safety or effectiveness differences between elderly patients and younger subjects. The product labeling is also required to disclose the total number, or percentage, of elderly patients in the referenced clinical studies. Furthermore, the package insert is to explain that while no overall safety or effectiveness differences were observed, physicians should not rule out greater sensitivity in some older individuals.

Listed below are statements that are to be included in the "Geriatric use" subsection of a package insert when no safety or efficacy differences can be discerned between the elderly and younger patients.

> "Of the total number of subjects in clinical studies of (name of drug), ___ percent were 65 and over, while ___ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out."

Once an application sponsor has conducted the required review of available geriatric clinical data, and comes to a decision that there are no discernible safety and efficacy differences in the various patient populations, the prescribed text cited above from § 201.57 (f) (10) (ii) (B) should be added to the labeling as soon as possible. There should be no requirement for review and approval by the FDA.

Comment Two

Section VI., Content and Format (Attachment 2), addresses specific filing requirements for supplemental applications.

Section VI. F. discusses data to support "Geriatric use" labeling.

> Item F. 3. reads, "Labeling that simply relocates information already in the approved labeling does not require a re-analysis of the original data that supported this information."

We concur with this requirement. However, we suggest that the guidance should also indicate that a change in labeling merely to reposition "currently approved text" should not require prior approval.

Wyeth-Ayerst Laboratories appreciates the opportunity to comment on the FDA's draft guidance for industry, "Content and Format for Geriatric Labeling." Should you have any questions, please contact the undersigned at Telephone No. (610) 902-3761 or FAX No. (610) 964-5972.

Sincerely,

WYETH-AYERST LABORATORIES

James J. O'Shaughnessy
Associate Director
U.S. Drug Regulatory Affairs

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Content and Format for Geriatric Labeling

I. INTRODUCTION

In a final rule published in the *Federal Register* on August 27, 1997 (62 FR 45313), FDA established the *Geriatric Use* subsection in the labeling for human prescription drug and biological products to provide pertinent information about the use of those products in the elderly. This guidance is intended to provide industry with information on submitting geriatric labeling of human prescription drug and biological products. This guidance discusses the following issues related to the submission of geriatric labeling:

- Who should submit revised labeling
- Implementation dates
- Description of the regulation and optional standard language in proposed labeling
- Content and format for geriatric labeling
- Applicability of user fees to geriatric labeling supplements

II. BACKGROUND

In 1997, FDA established the *Geriatric Use* subsection, as a part of the PRECAUTIONS section, in the labeling for human prescription drugs to include more complete information about the use of a drug or biological product in the elderly (persons aged 65 years and over) (21 CFR 201.57 (f)(10)). As a result, many application holders are required to submit geriatric labeling supplements under 21 CFR 314.70 or 601.12. These supplements require Agency approval prior to implementation except (1) in cases where the labeling change strengthens instructions for use

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[1] This guidance has been prepared by the Geriatric Subcommittee of the Medical Policy Coordinating Committee (MPCC), Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the content and format for geriatric labeling. The guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

as outlined in § 314.70(c)(2) or 601.12(f)(2)[2] and (2) for labeling changes submitted under § 201.57(f)(10)(ii)(A) (i.e., where insufficient data exist to determine whether the responses of geriatric patients to a drug are different from responses of younger patients).[3]

III. APPLICATION HOLDERS' RESPONSIBILITY FOR SUBMITTING REVISED LABELING

Under the geriatric labeling regulation, drug products fall into one of three categories with regard to submission of geriatric labeling supplements (Table 1). For drug products in the first category, which includes all marketed drug products with an approved new drug application (NDA), biologics license application (BLA), or product license application (PLA) and products marketed under an approved abbreviated new drug application (ANDA) where the ANDA product is the reference listed drug,[4] the submission is to include revised labeling and the data supporting the revision. For drug products in the second category, which includes marketed drug products for which there is no approved application, unmarketed drugs with an approved NDA, BLA, PLA or ANDA, and over-the-counter (OTC) drug products,[5] no submission is necessary. For drug products in the third category (i.e., marketed products with ANDAs that are not the reference listed product), revised labeling should be submitted based on the approved geriatric labeling of the reference listed drug product in the Orange Book when that drug's labeling is changed to include a *Geriatric Use* subsection.

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[2] See 62 FR 45313 at 45319 for further clarification.

[3] See 62 FR 45313 at 45316 for further clarification.

[4] See *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), FDA, sec. 1.4.

[5] For drugs that are available as both OTC and prescription drug products, the holders of applications for the prescription drug products are responsible for submitting revised geriatric labeling.

suggested. In this case, the application holder should submit a supplement under § 201.57(f)(10)(vi) that proposes an alternative statement or requests omission of the *Geriatric Use* subsection with the reasons supporting the omission.

The systemic absorption of topical ophthalmic drug products is usually minimal, and, consequently, systemic interactions are unlikely and have been observed very infrequently. As a general rule, clinical differences in response between the geriatric and younger populations, both from an efficacy and safety perspective, have not been demonstrated to occur in clinical studies of topical ophthalmic drug products. Although the geriatric labeling statements provided in the final rule will be appropriate for most drug products, they are not applicable for most ophthalmic drug products. Where clinical differences between the geriatric and younger populations are not demonstrated, sponsors of new drug applications for topical ophthalmic drug products should request an alternative statement for the *Geriatric Use* subsection under § 201.57(f)(10)(vi) such as "No overall differences in safety or effectiveness have been observed between elderly and younger patients."

VI. CONTENT AND FORMAT

In the *Federal Register* of February 11, 1998 (63 FR 6854), FDA amended the NDA format and content regulations to require safety and effectiveness data for important demographic subgroups, including age subgroups (21 CFR 314.50(d)(5)(v) and (vi)(a)). The regulation, effective August 10, 1998, also amends IND regulations to require sponsors to tabulate in their annual reports the number of subjects enrolled to date in clinical studies for drug and biological products according to certain subgroups, including age (21 CFR 312.33(a)(2)).

All supplements submitted to comply with the geriatric labeling final rule should be noted as "Geriatric Labeling Supplement" in the "Reason for Submission" block on FDA Form 356h for submissions to CDER or FDA Form 356h or other application forms for submissions to CBER. The following information should be included in the supplement in the order shown.

A. Cover Letter — A cover letter should include the following information.

1. Indicate that the submission is a geriatric labeling supplement.
2. Specify the paragraph(s) of the regulation pertinent to the supplement.
3. Include the user fee identification number if applicable.
4. If no user fee is required, explain the reason for the exception.

B. Detailed Table of Contents

C. Revised Labeling

1. Include a draft of the revised labeling.

2. Include a marked-up copy of the last approved labeling,[7] clearly showing all additions and deletions,[8] with annotations of where the supporting data are located in the submission.

3. Submissions to CBER should use form *FDA 2567 — Transmittal of Labels and Circulars*.

D. Applicable Regulatory Paragraph(s)

Indicate under which paragraph(s) in § 201.57(f)(10) (i) through (vi) the labeling is being revised and explain how the regulation applies .

E. User Fee

If applicable, the appropriate user fee needs to be submitted to the designated bank (21 U.S.C. 379(h)). A user fee cover sheet should be included in each submission (OMB No. 0910-0297). If no user fee is applicable, the sponsor should so indicate on the user fee cover sheet. (See section VII.)

F. Data to Support Geriatric Use Labeling

Data by type (e.g., efficacy, pharmacokinetic/pharmacodynamic, safety) should be presented, analyzed, and summarized, including data taken from published literature, using applicable parts of the format outlined in the *Format and Content of the Clinical and Statistical Sections of New Drug Applications* (FDA 1988). In addition, the following points should be noted.

1. The source of the data should be described (e.g., sponsor's clinical data,

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[7] Current labeling may differ from last approved labeling because the current labeling may include additions and/or deletions made before FDA approval (21 CFR 314.70(c) or 601.12(f)(2) and (3)) that have not yet undergone FDA review

[8] Show all changes being effected under 21 CFR 314.70(c) or 601.12(f)(2) and (3) that have not received an approval letter at the time of the Geriatric Use submission. Annotations for these changes should include the date and serial number or reference of the submission. It is not necessary to resubmit the data or analysis that supported the change.

medical literature, MedWatch).

2. Safety data should include the extent of exposure, duration of exposure, and adverse events.

3. Labeling that simply relocates information already in the approved labeling does not require a re-analysis of the original data that supported this information.

4. The analysis and source data that support any change from the currently approved labeling for the use of the drug product in the geriatric population should be submitted. For some supplements, the amount of potentially relevant data may be quite voluminous. In these instances, it will usually be useful to contact the FDA division where the application resides to discuss which data should be submitted.

5. The submission should state how the medical literature was searched (e.g., Medline), the beginning and ending dates covered by the search (month/year to month/year), and the date(s) the search was performed. A complete listing of literature reports reviewed by the sponsor should be included. [9] A summary of each literature article is not necessary. Only those articles that support the labeling change should be summarized as outlined in the *Format and Content of the Clinical and Statistical Sections of New Drug Applications*, and a copy of the article should be included in the submission. The FDA reviewer of the supplement may request copies of other literature articles included in the listing that are not provided in the submission.

VII. APPLICABILITY OF USER FEES TO GERIATRIC LABELING SUPPLEMENTS

The Prescription Drug User Fee Act of 1992 as amended by the Food and Drug Administration Modernization Act of 1997 provides no specific waivers of user fees for geriatric labeling supplements, although a supplement may qualify for a waiver based on one or more of the grounds for granting waivers listed in section 736(d) of the Act (21 U.S.C. 379h(d)). It is expected, however, that very few geriatric labeling supplements will require the payment of user fees because they will not require clinical data for approval, and only supplements for which

[9] The listing should be formatted as outlined in *Annals of Internal Medicine*, 126:36-47, 1997. (See discussion on References, pp. 40-42.)

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